REMARKS

Rejection of Claims 1-3(in part), 7-8 and 42 Under 35 U.S.C. §102(b)

Claims 1-4 are rejected under 35 U.S.C. §102(b) as being anticipated by Schwartz *et al.* According to the Office Action, Schwartz teaches an oligonucleotide compound comprising a central CG sequence, wherein the C can be modified to include cytosine arabinoside.

Schwartz describes an oligonucleotide compound comprising CG dinucleotide in which the C residue is modified by addition to C-5 and/or C-6 of an electron-withdrawing moiety, for example a halogen. Such a compound is termed by Schwartz as a "modified ISS" (see page 10, lines 6-9).

Schwartz does not place the presently claimed invention in the possession of a person of ordinary skill in the field. Unlike the present application, Schwartz does not demonstrate the modification of cytosine with anything but a halogen group, specifically 5-bromocytidine.

> Rejection for anticipation or lack of novelty requires as the first step in the inquiry, that all the elements of the claimed invention be described in a single reference. (Citation omitted.) Further, the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it. (Citation omitted.) *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990)

Unlike the present application, with its working example, Schwartz's mere mention of an arabinose sugar modification in a laundry list of possible modifications, with no working example, does not meet the criteria of *In re Spada*. Accordingly, Schwartz does not anticipate Claim 1. The remaining claims are dependent upon Claim 1 and are also not anticipated by Schwartz. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3(in part), 7 and 40 Under 35 U.S.C. §102(b)

Claims 1-6 are rejected under 35 U.S.C. §102(b) as being anticipated by Zuo *et al.* According to the Office Action, Zuo teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and the purine is a natural purine nucleoside.

Applicants' respectfully disagree. Zuo does not deal with immunostimulatory oligonucleotides or their administration. Applicants are aware that Federal Circuit decisions acknowledge that a prior art reference need not use the same language as a patent claim, that is,

that anticipation need not be "ipsissimis verbis." For example, in *Helifix, Ltd. v. Blok-Lok, Ltd.* (2000), the Federal Circuit noted that a publication that "does not expressly disclose in words" one or more elements of a patent's claims "might nevertheless be anticipating if a person of ordinary skill in the art would understand the [publication] as disclosing [the missing element or elements] and if such a person could have combined the [publication's] description of the invention with his own knowledge to make the claimed invention. (See In re Donohue, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985))".

One of ordinary skill in the art would not understand Zuo as disclosing immunostimulatory oligonucleotides or that the products of oxidative attack on 5-methylcytosine residues in DNA and the extent to which the products lead to deamination would lead to immunostimulatory oligonucleotides. Zuo teaches the use of radioactively labeled DNA co-polymers as a substrate and analytical HPLC as an assay system to characterize the formation of oxidative stress-induced damage to 5-methylcytosine in DNA and to determine its enzymatic repairability using DNA glycosylates as reagent enzymes (See Zuo at page 3239, col. 2, lines 33-37). This kind of damage does not lead to immunostimulatory oligonucleotides. Rather, as taught be Zuo, oxidative damage to cellular DNA has been shown to play a role in the pathology of Parkinson's disease, amyotrophic lateral sclerosis and cellular aging (see Zuo at page 3239, col. 1, lines 4-8).

In *Jamesbury Corp. v. Litton Industrial Products, Inc.* (1985), the Federal Circuit held that a jury instruction that a patent is invalid for lack of novelty if the prior art "disclosed substantially the same things" was erroneous. It noted that a verdict of invalidity for anticipation should be overturned when reasonable persons could not find the evidence clear and convincing that all the claim limitations were met by the prior art reference in question.

Since Zuo does not teach an immunostimulatory oligonucleotide compound comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3' wherein pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside, Zuo does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3 (in part), 7 and 41 Under 35 U.S.C. §102(b)

Claims 1-3 (in part), 7 and 41 are rejected under 35 U.S.C. §102(b) as being anticipated by Butkus *et al.* According to the Office Action, Butkus teaches a CpG composition that comprises an unnatural pyrimidine wherein the unnatural pyrimidine is N4-methylcytosine.

Applicants' respectfully disagree. Butkus does not deal with immunostimulatory oligonucleotides or their administration. The principal task of Butkus was to investigate DNA-methylases and their effects on cleavage of some methylated substrates. The cytosines in the DNA sequences taught in Butkus were primarily 5-methycytosine which are not immunostimulatory. Butkus does describe the discovery of a DNA-methylase producing N4-methylcytosine and thus preventing cleavage of host DNA. However, as discussed above (see response to rejection in view of Zuo), this dos not provide clear and convincing evidence that all the claim limitations are met by Butkus.

Since Butkus does not teach an immunostimulatory oligonucleotide compound comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3' wherein pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside, Butkus does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3 (in part), 6-7 and 39 Under 35 U.S.C. §102(b)

Claims 1-3 (in part), 6-7 and 39 are rejected under 35 U.S.C. §102(b) as being anticipated by Kreutzer *et al.* (hereinafter Kreutzer). According to the Office Action, Kreutzer teaches a CpG composition that comprises an unnatural pyrimidine, wherein the unnatural pyrimidine is 5-hydroxymethylcytosine

Applicants' respectfully disagree. Kreutzer does not deal with immunostimulatory oligonucleotides or their administration. The principal task of Kreutzer was to evaluate the mutagenic potency and specificity of the lesions 5-hydroxycytosine, 5-hydroxyuracil and uracil glycol by using a DNA system that served as a model for replication past an oxidized cytosine lesion. However, as discussed above (see response to rejection in view of Zuo), this dos not provide clear and convincing evidence that all the claim limitations are met by Kreutzer.

Since Kreutzer does not teach an immunostimulatory oligonucleotide compound comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3' wherein

pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside, Kreutzer does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 5-8 Under 35 U.S.C. §103(a)

Claims 5-8 are rejected under 35 U.S.C. §103(a) as unpatentable over Schwartz in view of Bennett *et al.* (hereinafter Bennett).

As described above, Schwatz does not disclose the claim invention because Schwartz does not meet the criteria of *In re Spada*. Bennett fails to provide that which Schwartz lacks. Bennett only describes antisense compounds capable of modulating, preferably inhibiting, expression of human bcl-x and of its isoforms. Bennett does not teach or suggest immunostimulatory oligonucleotides containing the CpG dinucleotide or the administration of such oligonucleotides to affect an immune response. One of ordinary skill in the art would have had no motivation to combine the descriptions in Schwartz and Bennett to arrive at the immunostimulatory oligonucleotide compounds of the instant claims. Therefore, the instant claims are nonobvious over Schwartz and Bennett. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above response, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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